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Original Research

Prevalence of diabetic nephropathy in Type 2 Diabetes Mellitus in rural communities of Guanajuato, Mexico. Effect after 6 months of Telmisartan treatment

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ABSTRACT

Objective: To determine the prevalence of Diabetic Nephropathy (DN) in patients with type 2 Diabetes Mellitus (T2DM) with over 5 years of evolution in rural communities of Guanajuato, Mexico, and evaluate the effects of an ARB treatment over 6 months in patients with DN.

Materials and methods: Patients of both sexes, 38–86 years, T2DM over 5 years of evolution and diagnosed with arterial hypertension (HT) after T2DM incidence. Monthly determination of microalbuminuria (MA), lipids, glucose, serum creatinine, and glycated hemoglobin (HbA1c). Estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula. A dose of 80 mg of Telmisartan was administered daily over 6 months.

Results: The total adult population of two rural communities (3609 subjects) was studied, 335 subjects had T2DM, among them 80 (with a prevalence of 24%) had DN and HT. Sixty-seven patients received Telmisartan, and showed significant improvement in all parameters studied.

Conclusions: A higher prevalence of DN than that reported in the Mexican National Health Survey (ENSANUT) was found. Further research is required in a larger population sample in order to confirm the results of Telmisartan treatment.

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Introduction

According to the Mexican National Health Survey ENSANUT, 2006, the national prevalence of Type 2 Diabetes Mellitus (T2DM) is 7%, being higher in women (7.3%) than in men (6.5%). The state of Guanajuato is below the national average, with a prevalence of 5.6% in adults aged 20 years or older, the prevalence is similarly higher in women (6.3%) than in men (4.7%) [1].

DN prevalence varies between 5% and 30% in patients with T2DM and MA is present in 40% of the subjects after 10 years of evolution. The risk of a progressive increase in albumin excretion to overt proteinuria within 6–14 years was 60–80% [2–6].

DN is the most common cause of end stage renal disease (ESRD) [2]. The MA in subjects with diabetes mellitus (DM) is a major

independent risk factor for cardiovascular events [7–9]. The incidence of ESRD in DN patients is 60% in Mexico. More than one in two ESRD patients in the State of Jalisco (Mexico) and the State of Morelos (Mexico) are reported to have diabetes. In Morelos, rates of diabetes in subjects 45–75 years and older are up to 1786 per million population according to the United States Renal Data System 2011 Annual Data Report [10].

The renin–angiotensin system plays a predominant role in the evolution of renal disease, not only by inducing changes in arterial pressure (BP) and glomerular hemodynamics [11], but also by increasing oxidative stress and promoting expression of pro-inflammatory genes and pro-fibrotic factors in mesangial cells and vascular smooth muscle [12], additionally, angiotensin II promotes mesangial cell and vascular smooth muscle proliferation, thus contributing to the enlargement of the arteriolar wall. Activated inflammatory cells, especially T cells, synthesize angiotensin, thereby reinforcing intrarenal angiotensin production [13]. Prospective controlled clinical studies show that angiotensin converter enzyme inhibitors (ACE), as well as angiotensin receptor

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blockers (ARBs), are able to stop or slow the progression of DN [14].

In subjects with T2DM, the eGFR decreases by approximately 6 mL/min per year [15], however, it has been observed that the addition of ACE inhibitors or ARBs to patients' treatment regimens, while not hypertensive, achieved a reduction in the rate of progression of the fall in eGFR, thereby stabilizing renal function for a prolonged period [14].

Moreover, metabolic control reduces catabolism and improves nutritional status, decreases or delays the onset of DN, and reduces glomerular hyperfiltration [16,17].

Given the significant annual increase in the number of patients with terminal DN, continued research aimed at early detection of DN and its treatment is required. Therefore, the present study was conducted in two rural communities in the state of Guanajuato in order to determine the prevalence of DN in T2DM patients with at least 5 years of disease evolution, and to study the possible renoprotective effect of an ARB (Telmisartan) at a dose of 80 mg/24 hr for a 6 month period.

Materials and methods

A quasi-experimental study was performed. To assess the prevalence of DN we included and evaluated all adult people of the rural communities of San Juan Jaripeo (N = 1835) and Colonia Morelos (N = 1774), in the State of Guanajuato, Mexico. All subjects had Social Security coverage, affiliated as follows: Mexican Health Institutes ISSSTE 223 (6%), IMSS (8%) and Popular Health Insurance (86%). All patients, independently of their medical affiliation, were treated in the Medical Primary Health Care Centers, during the period of November 2010 to April 2011. All 3609 patients of both sexes who had been diagnosed with T2DM over at least 5 years were included, they were under oral hypoglycemic agents or insulin, and were later diagnosed with HT which they controlled with various antihypertensive medications. Patients had no evidence of clinical nephropathy, or any other chronic disease, or general or local infectious disease. Their body mass index (BMI) was greater than 18.

One of the objectives in this study was to evaluate the effect of ARB treatment in patients with DM, therefore, those patients that required more than one drug to control hypertension were not included. Patients with less than 85% adherence to drug treatment, and those who did not attend two consecutive appointments were withdrawn from the study.

The DM treatment schedule remained unchanged, but the antihypertensive treatment was replaced by Telmisartan.

The study was approved by the Research Ethics Committee of Quetzalcoatl University, Mexico, according to the guidelines of the Ley General de Salud en Materia de Investigación [18]. All patients signed a letter of informed consent.

A clinical history was undertaken at the beginning of the study and the weight, height, BMI and BP at rest (performed in two readings within 15 minutes) were obtained, at the beginning, and after 3 and 6 months of the trial.

Glucose, creatinine, cholesterol, HDL, LDL (Ortho Clinical Diagnostic IVD), serum, and HbA1c (Hemoglobin 1AC Systems DCA) levels were determined after 12 hours of fasting. Quantitative MA (Ortho-Clinical-diagnostic IVD) was measured using the 411 COBA apparatus. Monthly urinalysis and quantitative determination of MA was performed using Combur Test ROCHE strips, MA was reported as mg/L according to Kumar et al. [19]. Similarly capillary glucose was performed using Combur Test ROCHE strips. The eGFR was calculated using the abbreviated MDRD formula [20], CKD was classified according to the guidelines of the KDOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice [21].

All patients received 80 mg of Telmisartan daily.

Statistical analysis

Data were tested for normality, descriptive statistics (measures of central tendency and distribution), frequency tables and percentages, inferential statistics, Friedman ANOVA for repeated measures were performed. The STATISTICA version 7 statistical package was used. Intention to treat analysis was not performed because all selected patients were treated with telmisartan, therefore no control group nor randomization were carried out.

Results

Out of a total of 3609 individuals, 335 had T2DM, 80 patients (23.8%) had DN and HT. Thirteen patients were removed, because they were lost to follow-up because of change of residency after the first appointment, leaving 67 patients for analysis (11 men, and 56 women), with an average age of 62 years (range of 38–88 years).

Table 1 shows the significant changes found in BP in both men and women after 6 months of Telmisartan treatment. Serum glucose decreased in men and women after treatment, even when the HbA1c decreased significantly only in women. The serum creatinine and eGFR values by the MDRD (65.9 ± 22.2) and the CKD-EPI (64.1 ± 19) formulas ($t = 0.510$, $p = 0.21$) showed a similar decrement in both sexes at the end of treatment. However, the values of MA decreased significantly only in women after treatment.

Fig. 1 shows the changes in the stratification of chronic renal disease after 6 months of treatment with Telmisartan. Twenty-seven patients were treated with Telmisartan in stages 3 and 4 before treatment, and after treatment there were only 19 patients. A total of 40 patients were in steps 1 and 2 before treatment, and increased to 44 after treatment. Four patients showed normal eGFR after treatment with Telmisartan.

Discussion

In this study population the prevalence of T2DM was found to be 9.28%, which is similar to that reported in the Mexican Encuesta Nacional de Salud y Nutrición 2012 [1].

The prevalence of DN in patients studied was 23.8%, lower than the prevalence of DN at 38.5–39.6% reported by Plantinga LC [22]. It is possible that the difference in DN prevalence is partially due to the fact that the majority of women in these communities are housewives entitled to the 'Oportunidades' (Opportunities) program, run by the Ministry of Health, and therefore regularly attend medical appointments [23,24].

The INNOVATION study shows the effect on the progression of DN using different doses of Telmisartan [11]. In this regard, the administration of 80 mg/day of Telmisartan showed that 16.7% of patients suffered a progression of renal damage, while 22.6% of patients receiving 40 mg/day of Telmisartan showed progression of DN, which is much lower than the figure observed (49.9%) in patients that received placebo.

This same study (INNOVATION) referred MA to 21.2% and 12.8% of the patients at the dose of 80 mg/day and 40 mg/day respectively.

Similar to the INNOVATION study results we found, in our study, that a dose of Telmisartan 80 mg/day administered for 6 months resulted in a significant decrease in the presence of MA in women (34.0 ± 13.5 mg/L to 20.6 ± 15.1 mg/L, $p < 0.00000$), and an increase in eGFR in both men and women (63.4 ± 20.2 mL/min to 72.0 ± 19.5 mg/mL, $p < 0.00000$). We also used the CKD-EPI formula, founding no differences with the abbreviated MDRD formula.

Several studies [25–37] have shown that the administration of Telmisartan in patients with T2DM and diabetic nephropathy, with or without hypertension, significantly improves glucose tolerance and insulin resistance. In this regard, we found a significant

Table 1
Clinical characteristics of the studied population

	Start	Three months	Six months	x ²	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)					
Men	69.3 ± 11	69.3 ± 11	69.3 ± 11		
Women	61.5 ± 12	61.5 ± 12	61.5 ± 12		
BMI (kg/m ²)					
Men	28.13 ± 2.9	28.10 ± 2.9	28.03 ± 2.9	4	<0.1
Women	29.13 ± 6.5	29.15 ± 7.2	29.21 ± 7.0	4	<0.1
SPB (mmHg)					
Men	165 ± 21.6	139.0 ± 15.0	128 ± 7.3	13.27	<0.001
Women	144.6 ± 21.9	127.3 ± 12.7	124.3 ± 8.8	38.4	<0.00000
DBP (mmHg)					
Men	92 ± 1.9	83.0 ± 7	84 ± 4.9	3.75	<0.1
Women	84.3 ± 10.8	80.5 ± 6.8	80.1 ± 6.5	2.9	<0.2
HbA1c (%)					
Men	8.7 ± 1.7	7.8 ± 1.3	7.7 ± 1.1	3.8	<0.1
Women	8.1 ± 2.1	7.3 ± 1.5	7 ± 1.1	20.9	<0.000
Serum glucose (mmol/L)					
Men	12.73 ± 6.13	9.13 ± 2.52	7.94 ± 2.1	6.83	<0.03
Women	10.8 ± 5.99	8.69 ± 3.31	7.8 ± 2.45	26.4	<0.00000
Cholesterol (mmol/L)					
Men	5.15 ± 1.78	4.99 ± 1.21	5.5 ± 1.45	0.19	0.9
Women	5.65 ± 1.68	5.23 ± 1.18	4.96 ± 1.01	18.59	<0.0000
Creatinine serum (mmol/L)					
Men	98.1 ± 26.5	99.01 ± 26.5	84.8 ± 17.2	13.8	<0.000
Women	91 ± 26.5	87.5 ± 26.5	80.4 ± 17.2	46.5	<0.00000
eGFR (mL/min/1.73m ²)					
Men	78.7 ± 28.0	78.6 ± 27.9	88.1 ± 23.22	20.60	<0.0000
Women	63.4 ± 20.2	63.3 ± 20.2	72.0 ± 19.5	78.5	<0.00000
Micro albuminuria (mg/L)					
Men	31 ± 14.9	31.4 ± 15.1	24.9 ± 21.3	2.36	0.3
Women	34.0 ± 13.5	29.1 ± 15.2	20.6 ± 15.1	53.37	<0.00000

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; eGFR, glomerular filtration estimated by MDRD formula.

improvement in the patient's metabolic control, with a significant decrease in serum glucose levels (196 ± 108.0 mg/dL to 140.6 ± 44.2 mg/dL, $p < 0.00001$), and in the HbA1c ($8.1 \pm 2.1 \pm 1.1\%$ to 7% , $p < 0.001$), as well as the concentration of total cholesterol (217.2 ± 64.5 to 190.7 ± 38.8 $p < 0.0001$). Masaki and colleagues identified that the effect of Telmisartan on insulin resistance is seen only in overweight and obese patients [25], which may explain our findings because the women in this study were more overweight or obese than men.

The study was conducted in rural municipalities in the state of Guanajuato, where the female population is greater than the male population. Almost all women in these communities are housewives, and are mostly the beneficiaries of the Opportunities program, and therefore regularly attend medical appointments [23,24]. Men are mainly agricultural workers, or have migrated to the United States, which means that they cannot attend appointments [24]. Moreover, other factors must also be considered that may cause poor adherence to medical treatment such as the use of medicinal plants, low education levels, and lack of information [38].

Finally, we must state that there are some limitations to our study; although measuring urinary creatinine allows to correct potential variable concentration during the day, we did not measure urinary creatinine and therefore we did not calculate the ACR. Another limitation is that we cannot infer causality because this is not a randomized clinical trial.

Conclusions

The prevalence of T2DM was 9.28% and for DN was 23.8%. We found improvement of systolic blood pressure, urinary albumin excretion, eGFR, and the metabolic control after Telmisartan treatment, in overweight and/or obese T2DM patients. Telmisartan effect should be evaluated in T2DM with normal weight.

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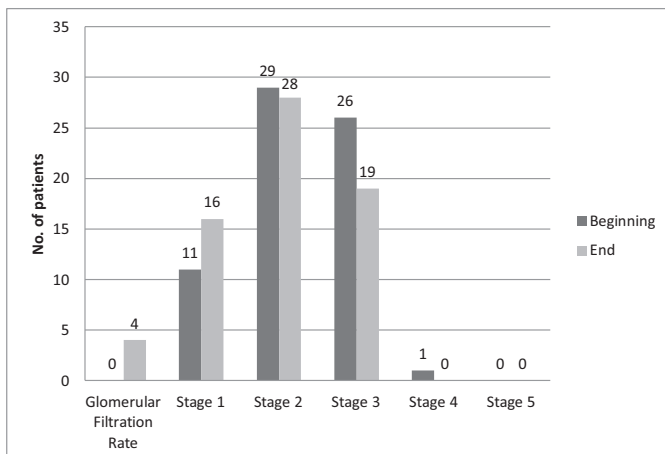


Figure 1. Comparison of the number of stratification cases, according to the K/DOQI at the beginning and the end of the study.

Conflict of interest

The authors declare they have no conflict of interest.

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